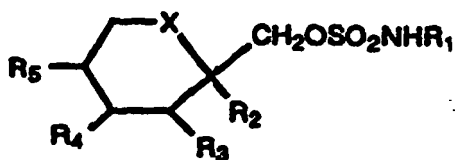




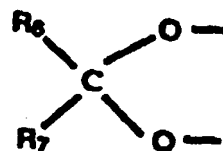
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>(51) International Patent Classification <sup>6</sup> :</b><br><b>A61K 31/35 // 31/18, 31/34</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 98/15270</b><br><b>(43) International Publication Date:</b> 16 April 1998 (16.04.98)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>(21) International Application Number:</b> PCT/US97/12350<br><b>(22) International Filing Date:</b> 16 July 1997 (16.07.97)<br><b>(30) Priority Data:</b><br>60/027,687                      8 October 1996 (08.10.96)                      US<br><b>(71) Applicant:</b> ORTHO PHARMACEUTICAL CORPORATION [US/US]; Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US).<br><b>(72) Inventors:</b> SHANK, Richard, P.; 551 Village Circle, Blue Bell, PA 19422-1636 (US). WILD, Kenneth; 186 Municipal Road, Pipersville, PA 18947 (US).<br><b>(74) Agents:</b> CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US). |           | <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>With international search report.</i> |

(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING NEUROPATHIC PAIN



(I)



(II)

## (57) Abstract

The present invention describes a method for treating neuropathic pain comprising administering to a mammal afflicted with such condition a therapeutically effective amount for treating such condition of a compound of formula (I), wherein: X is CH<sub>2</sub> or oxygen; R<sub>1</sub> is hydrogen or alkyl; and R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or lower alkyl and, when X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may be alkene groups joined to form a benzene ring and, when X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of formula (II), wherein R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring, particularly topiramate.

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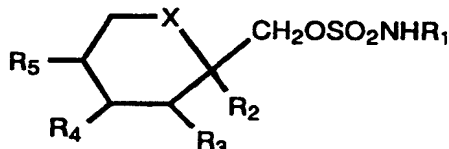
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| EE | Estonia                  |    |                                          |    |                                              |    |                          |

## ANTICONVULSANT DERIVATIVES USEFUL IN TREATING NEUROPATHIC PAIN

## 5 BACKGROUND OF THE INVENTION

Compounds of Formula I:



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are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem.* 30, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L.

15 Bioorganic & Medicinal Chemistry Letters 3, 2653-2656, 1993). These compounds are covered by US Patent No.4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive  
20 therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, *Epilepsia* 36 (S4) 33, 1995), and is currently marketed for the treatment of simple  
25 and complex partial seizure epilepsy with or without secondary generalized seizures in Great Britain, Finland, Sweden and Switzerland. Applications for regulatory approval are presently pending in numerous countries throughout the world including but not limited to the United States.

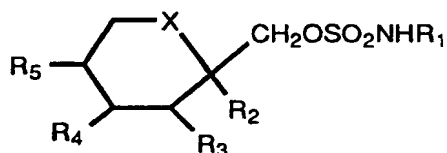
Compounds of Formula I were initially found to possess anticonvulsant  
30 activity in the traditional maximal electroshock seizure (MES) test in mice (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., *Epilepsia* 35 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently topiramate was found to  
35 effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M.

SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24 73-77, 1996).

Recent preclinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate is effective in treating some other disorders. One of these is neuropathic pain.

## DISCLOSURE OF THE INVENTION

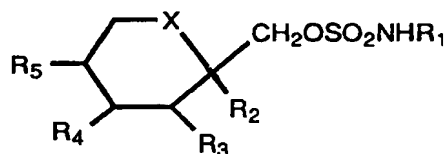
Accordingly, it has been found that compounds of the following formula I:



wherein X is O or CH<sub>2</sub>, and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined hereinafter are useful in treating neuropathic pain.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIEMENTS

The sulfamates of the invention are of the following formula (I):

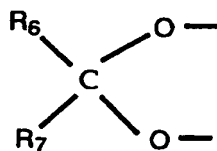


wherein

X is CH<sub>2</sub> or oxygen;

R<sub>1</sub> is hydrogen or alkyl; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or lower alkyl and, when X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may be alkene groups joined to form a benzene ring and, when X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of the following formula (II):



wherein

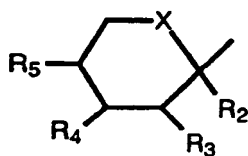
R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

R<sub>1</sub> in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R<sub>4</sub> and R<sub>5</sub> are defined by the alkatrienyl group =C-CH=CH-CH=.

A particular group of compounds of formula (I) is that wherein X is oxygen and both R<sub>2</sub> and R<sub>3</sub> and R<sub>4</sub> and R<sub>5</sub> together are methylenedioxy groups of the formula (II), wherein R<sub>6</sub> and R<sub>7</sub> are both hydrogen both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R<sub>6</sub> and R<sub>7</sub> are both alkyl such as methyl. A second group of compounds is that wherein X is CH<sub>2</sub> and R<sub>4</sub> and R<sub>5</sub> are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R<sub>2</sub> and R<sub>3</sub> are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula RCH<sub>2</sub>OH with a chlorosulfamate of the formula ClSO<sub>2</sub>NH<sub>2</sub> or ClSO<sub>2</sub>NHR<sub>1</sub> in the presence of a base such as potassium *n*-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



(b) Reaction of an alcohol of the formula RCH<sub>2</sub>OH with sulfurylchloride of the formula SO<sub>2</sub>Cl<sub>2</sub> in the presence of a base such as triethylamine or pyridine at a

temperature of about  $-40^{\circ}$  to  $25^{\circ}$  C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula  $\text{RCH}_2\text{OSO}_2\text{Cl}$ .

The chlorosulfate of the formula  $\text{RCH}_2\text{OSO}_2\text{Cl}$  may then be reacted with an amine of the formula  $\text{R}_1\text{NH}_2$  at a temperature of about  $40^{\circ}$  to  $25^{\circ}$  C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

(c) Reaction of the chlorosulfate  $\text{RCH}_2\text{OSO}_2\text{Cl}$  with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula  $\text{RCH}_2\text{OSO}_2\text{N}_3$  as described by M. Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein  $\text{R}_1$  is hydrogen by catalytic hydrogenation, e.g. with a noble metal and  $\text{H}_2$  or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula  $\text{RCH}_2\text{OH}$  may be obtained commercially or as known in the art. For example, starting materials of the formula  $\text{RCH}_2\text{OH}$  wherein both  $\text{R}_2$  and  $\text{R}_3$  and  $\text{R}_4$  and  $\text{R}_5$  are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a  $\text{R}_6\text{COR}_7$  ketone or aldehyde with fructose at a temperature of about  $25^{\circ}$  C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Volaa 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae  $\text{RCOOH}$  and  $\text{RCHO}$  may be reduced to compounds of the formula  $\text{RCH}_2\text{OH}$  by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about  $0^{\circ}$  to  $100^{\circ}$  C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the process disclosed in 5,387,700, which is incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below

and above the plane of the drawing, of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

5           The activity of the compounds of formula I in treating neuropathic pain was first evidenced in preclinical studies conducted to evaluate the efficacy of topiramate in an animal model of neuropathic pain. This model was developed and first described by S.H. KIM and J.M. CHUNG, Pain 50 355-363, 1992, and is termed the "Kim and Chung model".

10

          Male, Sprague-Dawley rats, weighing between 150-250 grams, have the L5 and L6 (lumbar region) spinal nerves tightly ligated (tied-off with surgical thread) between the spinal cord and entry into the sciatic nerve (in the hind leg) on one side of their body only. This procedure results in  
15   allodynia (a painful response to normally innocuous stimuli) and hyperalgesia (an exaggerated response to normally painful stimuli) in the hind paw on the same side of the body as the ligation (affected paw), but does not render the paw useless. The subjects are still capable of walking and using the affected paw. Within a few days the subjects are placed in  
20   elevated observation chambers (approximately 4" x 6" x 10") having wire mesh floors. Graded pressure is presented to a localized area on the bottom of the paw via the use of von Frey hairs (monofilaments which are calibrated to bend under a certain amount of pressure, ranging from 0.41 to 15.1 g). Tactile allodynia is measured by recording the various pressures at which  
25   the affected paw is withdrawn from the graded stimuli according to the procedure of S.R. CHAPLAN et al. (J. Neurosci. Meth. 53 55-63, 1994). Animals respond to 12-15 grams of pressure on their non-affected paws, whereas Kim and Chung model animals respond to 1-3 grams of pressure on their affected paw. The cutoff value for a rat to be included in this study  
30   was a response to 4 grams or less of pressure on the affected paw within 7 days after surgery.

          Three doses of topiramate (3, 10, and 30 mg/kg) were tested for oral activity against neuropathic pain in the Kim and Chung model; an oral dose of ULTRAM™  
35   (tramadol hydrochloride, 60 mg/kg) was tested as a positive control (D. BIAN et al., Analgesia 2 57-62, 1996). As expected, tramadol hydrochloride (60 mg/kg, p.o.) decreased the sensitivity of affected paws of Chung model rats from 3.0 grams to a peak of 13.9 grams at 2 hours after dosing; sensitivity returned back to 4.6 grams

by 8 hours (n=4). Topiramate (30 mg/kg, p.o.) also decreased the sensitivity of affected paws of Chung model rats from 3.0 grams to a peak of 8.9 grams at 1 hour; sensitivity returned slowly to 6.3 grams at 8 hours and remained at 5.6 grams 24 hours after dosing (n=4). Smaller doses of topiramate had less effect, altering the sensitivity to a maximum of 2.9 grams at 4 hours (3 mg/kg, p.o.) and 5.2 grams at 8 hours (10 mg/kg, p.o.), but these effects were not deemed significant in this study (n=4 each).

The long-lasting anti-allodynic effect of topiramate in this animal model of neuropathic pain indicates that it may be useful for the treatment of neuropathic pain in humans.

For treating neuropathic pain, a compound of formula (I) may be employed at a daily dosage in the range of about 50 to 400 mg administered orally, usually in two divided doses, for an average adult human. A unit dose would contain about 25 to 200 mg of the active ingredient.

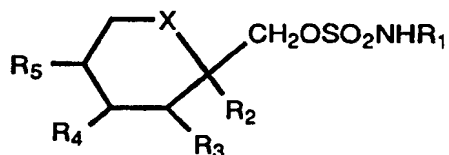
To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 25 to about 200 mg of the active ingredient.

## WHAT IS CLAIMED IS:

1. A method for treating neuropathic pain comprising administering to a mammal  
 5 afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:

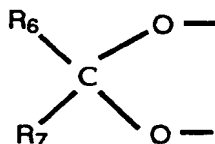


10 wherein

X is CH<sub>2</sub> or oxygen;

R<sub>1</sub> is hydrogen or alkyl; and

- 15 R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or lower alkyl and, when X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may be alkene groups joined to form a benzene ring and, when X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of the following formula (II):



20

wherein

R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

- 25 2. The method of claim 1 wherein the compound of formula I is topiramate.
3. The method of claim 1, wherein the therapeutically effective amount is of from about 50 to 400 mg.
- 30 4. The method of claim 1, wherein the amount is of from about 25 to 200 mg.

# INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/US 97/12350

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/35 //A61K31/18,A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                           | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A          | US 4 513 006 A (B. E. MARYANOFF) 23 April 1985<br>cited in the application<br>see the whole document<br>---                                                                                                  | 1-4                   |
| A          | SANDER: "The new anti-epileptic drugs :<br>their current role in the management of<br>epilepsy"<br>EUR. J. BIOCHEM.,<br>vol. 3 suppl., no. 3, August 1996,<br>pages 15-20, XP002043894<br>see page 18<br>--- | 1-4                   |
| A          | "Topiramate"<br>DRUGS FUTURE,<br>vol. 21, no. 4, 1996,<br>pages 463-465, XP002043895<br>see the whole document<br>---                                                                                        | 1-4                   |
| -/-        |                                                                                                                                                                                                              |                       |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

17 October 1997

Date of mailing of the international search report

31.10.97

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Authorized officer

Gac, G

# INTERNATIONAL SEARCH REPORT

Int. l. Application No  
PCT/US 97/12350

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                           | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------|-----------------------|
| P,A        | WO 97 13510 A (NEW ENGLAND MEDICAL CENTER<br>HOSPITAL INC.) 17 April 1997<br>see the whole document<br>----- | 1-4                   |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 12350

## B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 1-4  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. .nal Application No

PCT/US 97/12350

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